Children Are Not Just Small Adults

Choosing AEDs in Children

Natrujee Wiwattanadittakun, MD

Neurology division, Department of Pediatrics,
Chiang Mai University Hospital, Chiang Mai University

20th July, 2018
Treatment Goals

✧ Seizure freedom
✧ No adverse side effects
✧ Monotherapy
✧ Easy regimen to follow

AEDs Selection

- Efficacy profile
- Mechanism of action
- Epilepsy type
- Side effect
- Co-morbidities
- Drug-drug interaction
- Ease of use
- Cost; brand VS generic
Special Consideration in Children

- Decision to treat —> Accurate Diagnosis!
- Febrile seizure?
- Think Epilepsy Syndrome
- Contraindication/safety profile
- Etiology: presumptive metabolic disease, genetic
- Specific seizure type
Pediatric data

- 70% of recurrences were within 6 months of the first seizure, 77% by 1 year, and 90% by 2 years

- Recurrent rates were higher in children with abnormal neurological examination, focal spikes on EEG, and complex partial seizures

- Recommendation: No treatment until second seizure; > 50% will never have another seizure again

Some drugs have superior efficacy and others drugs worsen seizure control.

If you know the epilepsy syndrome you can

- Predict long-term prognosis of childhood onset epilepsy
- Pharmacoresponsive
- Remits or require life-long therapy
Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines

*Comprehensive Epilepsy Center, Division of Neurology, Cincinnati Children’s Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, U.S.A.; †Institution for Clinical Neuroscience, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; ‡Department of Neurology, The Children’s Hospital and Harvard Medical School, Boston, Massachusetts, U.S.A.; §Division of Biostatistics and Study Methodology, Center for Translational Science, Children’s National Medical Center, Washington, District of Columbia, U.S.A.; ¶Department of Neurology, University of Campinas (UNICAMP), Hospital das Clínicas, Campinas, Sao Paulo, Brazil; #Department of Neurology, Kuopio Epilepsy Center, Kuopio University Hospital, Kuopio, Finland; **Department of Neurology, Yale University School of Medicine, Yale New Haven Hospital, New Haven, Connecticut, U.S.A.; ††Comprehensive Epilepsy Center, New York University Langone Medical Center, New York, New York, U.S.A.; ‡‡Clinical Pharmacology Unit, Institute of Neurology, IRCCS C. Mondino Foundation, University of Pavia, Pavia, Italy; and §§Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden
## Efficacy Profile

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Class I studies</th>
<th>Class II studies</th>
<th>Class III studies</th>
<th>Level of efficacy for initial monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with partial-onset seizure</td>
<td>4</td>
<td>1</td>
<td>34</td>
<td>Level A: CBZ, LEV, PHT, ZNS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: GBP, LTG, OXC, PB, TPM, VGB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: CZP, PRM</td>
</tr>
<tr>
<td>Children with partial-onset seizures</td>
<td>1</td>
<td>0</td>
<td>19</td>
<td>Level A: OXC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, PB, PHT, TPM, VPA, VGB</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: CLB, CZP, LTG, ZNS</td>
</tr>
</tbody>
</table>

## Efficacy Profile

<table>
<thead>
<tr>
<th>Seizure Type</th>
<th>Class I studies</th>
<th>Class II studies</th>
<th>Class III studies</th>
<th>Level of efficacy for initial monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults with generalized onset tonic–clonic seizures</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: GBP, LEV, VGB</td>
</tr>
<tr>
<td>Children with generalized onset tonic–clonic seizures</td>
<td>0</td>
<td>0</td>
<td>14</td>
<td>Level A: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level B: None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level C: CBZ, PB, PHT, TPM, VPA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Level D: OXC</td>
</tr>
</tbody>
</table>

Children with Absence Seizure

- Level A: Ethosuximide, valproate
- Level C: Lamotrigine (1 Class I, 7 Class III studies)
- Others: clobazam, clonazepam, leveliracetam, topiramate, zonisamide, gabapentin
- Consider: Teenage girl, side effect

Benign Epilepsy with Centrotemporal spikes (BECTs)

- Level C: carbamazepine, valproate
- Level D: Gabapentin, levetiracetam, oxcarbamazepine, STM (3 Class III studies)
- Most of them may not need AEDs (infrequent, nocturnal seizures, onset close to the age of remission)
- Carbamazepine may aggravate new type of seizure/continuous spike-waves during slow wave sleep

Juvenile Myoclonic Epilepsy (JME)

- Level D: Topiramate, valproate (1 Class III studies)
- Others: levetiracetam, zonisamide, lamotrigine, clobazam, clonazepam

Efficacy

- Some drugs worsen seizure control
  - Carbamazepine: absence seizure
  - Phenytoin may worsen myoclonic seizure
Mechanism Of Action

Not illustrated:
- Vigabatrin → ↓GABA degradation and drugs with multiple mechanisms:
- Valproate → ↑GABA turnover, ↓Na⁺ channels, ↓NMDA receptors
- Topiramate → ↓Na⁺ channels, ↓AMPA/kainate receptors, ↑GABA₆ receptors
- Felbamate → ↓Na⁺ channels, ↑GABA₆ receptors, ↑NMDA receptors
Dravet syndrome

- Severe myoclonic epilepsy of infancy
- Normal infant
- Seizure one less than 1 year old
- Febrile status epilepticus: GTCs, hemiclonic
- Later afebrile seizure; myoclonic, tonic, atypical absence
- Developmental regression/plateau
Dravet syndrome

- 80% due to **SCN1A mutation**; sodium channel called NaV1.1

- EEG: First year normal, 2-5 years: generalized spikes/polyspike, multifocal

- Drug of choices: valproate, topiramate, clobazam

- Avoid: Sodium channel blocker ****** phenytoin, carbamazepine, lamotrigine, vigibatrin

Adverse Effects

- All antiepileptic drugs; drowsiness, dizziness, and rash; drugs act on the GABA system tend to be more sedating

- Cognitive disturbance: phenobarbital, topiramate, carbamazepine

- Phenytoin-induced gingival hyperplasia increased in children and poorer oral hygiene

Casetta I. Neuroepidemiology 1997;16;296-303.
Serious Adverse Effects

- Valproate-induced fatal hepatotoxicity
  - Young age
    - Age 21-40 years 1:31000
    - Age < 2 years 1:600 ****
  - Polytherapy

Pharmacokinetic Fun Facts

- Absorption
  - Phenytoin: Age-dependent: Less than 3 months old poor absorption/unpredictable and may not reliable until 5 years old

- Distribution
  - Phenytoin: $V_d$ declined with age

Matsukura M, Dev Phamaco There 1984;7;160-8.
Pharmacokinetic Fun Facts

Phenytoin and not fosphenytoin is what is clinically relevant. Fosphenytoin is water-soluble and is formulated as a nontoxic, parenteral solution. The pharmacokinetics of phenytoin derived from fosphenytoin are identical to phenytoin given directly [Leppik et al., 1989].

Fosphenytoin is packaged as milligram phenytoin equivalents and is well tolerated when given intramuscularly. Fosphenytoin absorption, not its conversion to phenytoin, appears to be the rate-limiting step in achieving therapeutic phenytoin levels. The mean half-life of fosphenytoin is 8 minutes after IV administration [Donn et al., 1987; Gerber et al., 1988; Leppik et al., 1989] and 33 minutes after intramuscular injection [Leppik et al., 1990]. Age does not affect the phosphatase enzyme responsible for the conversion of fosphenytoin to phenytoin. Fosphenytoin is more avidly bound to albumin, compared with phenytoin, resulting in brief increases of free phenytoin concentrations after infusion [Hussey et al., 1990; Jamerson et al., 1990].

Unlike phenytoin, fosphenytoin can be given intramuscularly and avoids serious tissue necrosis from extravasation of IV phenytoin. Its major uses are treatment of status epilepticus and maintenance therapy when oral administration is not possible.

Lacosamide

Lacosamide (known as harkoside in earlier studies) was approved for use in the United States during 2009. It is completely and rapidly absorbed with a bioavailability of 100 percent [Hovinga, 2003]. Lacosamide appears to follow linear pharmacokinetics and its $C_{\text{max}}$ is between 1 and 4 hours after an oral dose [Hovinga, 2003]. There does not seem to be a food effect on lacosamide pharmacokinetics [Kellinghaus, 2009]. Protein binding has been shown to be less than 15 percent. Lacosamide is metabolized to an inactive desmethyl metabolite, which is then cleared along with the parent drug via the kidney. Lacosamide is not approved for use in young children at this time; however, there is at least one clinical trial that is investigating the safety and pharmacokinetics in children with partial seizures between the ages of 2 and 17 years. Doses being studied are 8–12 mg/kg/day.

Lamotrigine

Lamotrigine has a bioavailability approaching 100 percent. Its $T_{\text{max}}$ occurs 2–3 hours after administration of a single oral dose. With doses in the range of 15–240 mg, $T_{\text{max}}$ and area under the curve increase with increasing doses of lamotrigine. There does not seem to be a food effect on lamotrigine pharmacokinetics [Kellinghaus, 2009]. Protein binding has been shown to be less than 15 percent. Lamotrigine is metabolized to an inactive metabolite, which is then cleared along with the parent drug via the kidney. Lamotrigine is not approved for use in young children at this time; however, there is at least one clinical trial that is investigating the safety and pharmacokinetics in children with partial seizures between the ages of 2 and 17 years. Doses being studied are 8–12 mg/kg/day.

Phenytoin concentration ($\mu$g/mL)

Fig. 59-4

Phenytoin dosing requirements in children. Curves were derived from data of maximum capacity of the enzyme system to metabolize phenytoin ($V_{\text{max}}$) and the plasma concentration at which the rate of metabolism is 50 percent of maximum capacity for children ($K_m$) (see Table 59-2).

Fig. 59-5

Schematic of steady-state plasma concentrations of an antiepileptic drug when a particular antiepileptic drug is given alone or in combination with other medications. (We wish to thank Nina Graves, Pharm.D., for her contribution to this figure.)

<table>
<thead>
<tr>
<th>Age</th>
<th>Maintenance (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>4-6</td>
</tr>
<tr>
<td>0.25-3 years</td>
<td>6-10</td>
</tr>
<tr>
<td>4-6 years</td>
<td>5-7</td>
</tr>
<tr>
<td>7-9 years</td>
<td>4-7</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>4-6</td>
</tr>
</tbody>
</table>
Pharmacokinetic Fun Facts

- Elimination
  - Renal elimination of drugs and metabolite lower than adult until 6 months old
  - Metabolism/drug clearance faster than adult; required more frequent dosage
    - Phenytoin: half life 5-14 hours in children; require two divided dose
    - Carbamazepine: half life 5-27 hours in children require three divided dose

Fenichel’s Clin Pediatric Neurology 2013; 36-42.
# Drug Disposition at Different Ages

<table>
<thead>
<tr>
<th></th>
<th>Neonate</th>
<th>Infants, Children</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>↓</td>
<td>↑</td>
<td>A</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>↓</td>
<td>↓</td>
<td>↓ ➔ A</td>
</tr>
<tr>
<td>Metabolism</td>
<td>↓</td>
<td>↑</td>
<td>↓ ➔ A</td>
</tr>
<tr>
<td>Excretion</td>
<td>↓</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

A = Adult level

Ease of Use

- IV VS oral: PHT, PB, VPA, LEV, LCM
- Quick-up titration: phenytoin, phenobarbital, valproate, levetiracetam, zonisamide, lacosamide
- Not: CBZ, lamotrigine
- Tablet/solution/sprinkles
Tablet

- Crush oral solids form/disguise the taste with a small volume of flavoured drink or food

- Be aware some drugs lose their properties

- Extemporaneous preparation (small dose)

- Are you sure about stability, amount of the drug and bioavailability?
Don’t forget

- Caregivers should be thoroughly educated
  - Drug administration technique
  - Who/how/how many times
  - Adverse effect/drug allergy